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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,105	04/03/2001	Michael W. Russell	D6321	3233

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EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,105	RUSSELL ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the Appeal Brief filed on December 8, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 1-3, 6, and 24-29 are pending in the application and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claim 1 submitted on 2/23/03 recites, "said immune response is selected from the group consisting of ...the development of cytotoxic T cells and *immunological tolerance to the antigen sequence*". Accordingly, claims 1-3, 6 are rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to teach inducing tolerance to a recombinant immunogen as now claimed. Thus the subject matter concerning immunological tolerance is now considered to be new matter.

MPEP 2163.02 teaches "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". In the instant case, the specification as originally filed describes inducing an immune response with a recombinant immongen, and it fails to teach *suppressing* an immune response with a recombinant immunogen (tolerance to an antigen) as now claimed. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed 2/23/03 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132

states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added). Applicants are invited to specifically point out where in the original disclosure the support can be found.

To the extent that the claimed methods are not described in the instant disclosure, claims 1-3, 6 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Claims 1-3, 6, and 24-29 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing or enhancing an immune response in general by the mucosal route of administration of a recombinant immunogen comprising a fusion protein of an antigen of interest fused to the A2/B subunit of the type II heat-labile enterotoxin, does not reasonably provide enablement for inducing/enhancing a cytotoxic T cell response, a Th1 type of response, or

immunological tolerance to the antigen by any route of administration of the fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claim 1 recites inducing the development of cytotoxic T cells, and immunological tolerance to an antigen with a fusion protein comprising an antigen of interest fused to the A2/B subunit of the type II heat-labile enterotoxin, claims 24 and 27 call for increasing Th1 response and cell-mediated immunity with said fusion protein, however, the disclosure of the specification fails to support these claims.

In view of the guidance provided in the specification, the specification fails to provide any support showing that a cytotoxic T cell response is indeed induced or enhanced, none of the figures showing a CTL response. In figure 3c, the only figure in

the specification that directly illustrating the potential differentiation of Th1 or Th2 responses with the fusion protein SBR-LTIIA2/B by assaying the types (IgG1/IgG2) of SBR-specific antibodies shows that SBR-LTIIA2/B induced a significantly higher IgG1 antibody response (i.e. a Th2 response) compared to the IgG2a antibody response (a Th1 response). Accordingly, the teaching of the specification contradicts the claimed invention.

Figure 5 of the specification has a caption of B7-denpendent co-stimulation of T cells, however, a closer look would find that the experiments were conducted on B lymphocytes *in vitro*, that the LTIIaA2/B appears to be independent of B7 co-stimulation, and even assuming that the LTIIaA2/B response is B7 dependent, the figure only shows the activation of B cells, not a T cell, and not a cytotoxic T cell.

Figures 7 and 8 of the specification illustrate the activation of antigen presenting cells (monocyte-derived dendritic cells) via assaying CD40L and cytokine produced, they do not provide any evidence for the type of T cell responses induced, nor whether CTL response is present. Further, figures 7 and 8 fail to show the effect of the LTIIaA2/B, the experiments only use LT-IIa or LT-IIb in the fusion protein.

Likewise, figures 6A-6E only show the effect of LT-IIa and LTIIb, not the LTIIaA2/B, and the resulting cytokine production fail to discriminate the type of responses produced. For example, IL-2 and TNF-alpha could increase in both Th1 and Th2 type of T cell responses.

In view of the knowledge of the skilled in the art, *Rappuoli et al* teach, "THIS POLARIZATION IN THE T-CELL RESPONSE IS MUCH LESS PRONOUNCED WHEN LT IS USED AS A

MUCOSAL ADJUVANT, WITH BOTH TH1 AND TH2 CELLS BEING ACTIVATED. IN ADDITION, RECENT STUDIES SUGGEST THAT LT MUTANTS WITH ONE SINGLE AMINO ACID SUBSTITUTION IN THE A SUBUNIT HAVE DIFFERENT BEHAVIOUS IN THE ACTIVATION OF THE CD CELL SUBPOPULATION". The specification fails to disclose any evidence that is contrary to what was known in the art as taught by *Rappuoli et al*, and apparently one cannot predictably determine the immunoadjuvant effect of the LTIIaA2/B using the results of LT-II whole molecule.

Given the broadest reasonable interpretation, the claims encompass administering the recombinant immunogen via any route such as those recited in claim 6. However, it is well known in the art that LT and CT are mucosal adjuvants such as those taught by *Rappuoli et al*. The specification only uses mucosal routes to deliver the recombinant immunogen, it fails to teach that a mucosal adjuvant could be used in a non-mucosal route, such as intramuscular route, and achieve the effects that were observed via mucosal delivery. Given the knowledge of the skilled in the art and the unpredictability in the art, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

With respect to inducing tolerance to the antigen, tolerance refers to the specific failure of a normally responsive individual to make an immune response to a known antigen. It results from previous contact with the antigen by an immunologically immature individual (fetus or neonate) or by an adult exposed to extreme high-dose or low-dose antigen, or by exposure to radiation, antimetabolites, antilymphocytic serum, etc. (PubMed, Mesh term database), it depends on the types and levels of immunogen, and it depends on the interaction of many different types of immune cells, such as

antigen presenting cells and different subtypes of T cells, along with cytokines, and co-stimulatory molecules. *Malone et al* (US 6110898) teach delivering a recombinant immunogen via the mucosal immune system. "MUCOSAL ANTIGEN PRESENTATION CAN BE ASSOCIATED WITH EITHER IMMUNOLOGIC STIMULATION OR INDUCTION OF TOLERANCE", "LIKE THE SYSTEMIC IMMUNE COMPARTMENT, THE COMMON MUCOSAL IMMUNE SYSTEM REQUIRES MECHANISMS FOR SELECTIVE SWITCHING BETWEEN THE EXPANSION OF EFFECTOR CELLS AND THE INDUCTION OF TOLERANCE", "THE MECHANISM(S) INVOLVED IN SWITCHING BETWEEN INDUCTION OR SUPPRESSION OF MUCOSAL IMMUNE RESPONSES REMAIN TO BE RESOLVED"(Column 2). The specification fails to teach how the A2/B subunit of LT-II influences the switch between induction and suppression of an immune response, fails to teach how to switch from the induction of the immune response as taught in the specification to suppression of such immune response using the same recombinant immunogen, thus, fails to provide an enabling disclosure for what is now claimed.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* induction of Th1 type and cytotoxic T cell responses, and induction of tolerance, and doing by any route of administration, the lack of direction provided by the specification as well as the absence of working examples with regard to the breadth of the claims directed to the use of any recombinant antigen by any route of administration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention commensurate with the scope of the claim.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 25, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "the antigen sequence". There is insufficient antecedent basis for this limitation in the claim.

Claims 2, 25, and 28 recite the limitation "said antigen of interest". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1-3, 6, and 24-29 under 35 U.S.C. 103(a) as being unpatentable over *Toida et al* (Infect Immunity 1997;65:909-15), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61) is withdrawn because the combined teachings of the prior art of record fail to fairly suggest the immune adjuvant effect of the A2/B subunit of the type II heat-labile enterotoxin.

The prior rejection of claims 1-3, 6, and 24-29 under 35 U.S.C. 103(a) as being unpatentable over *Russell et al* (US 6,030, 624), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61)) is withdrawn because the combined teachings of the prior art of record fail to fairly suggest the immune adjuvant effect of the A2/B subunit of the type II heat-labile enterotoxin.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
February 23, 2004